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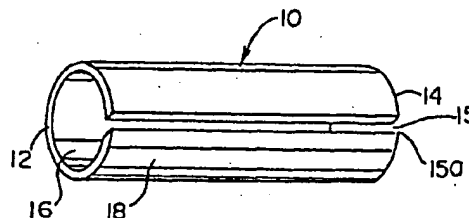
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(54) Title: DRUG DELIVERY DEVICE FOR STENT

(57) Abstract

A device adapted for mounting on a stent, the device comprising a sheath being made of polymeric material that includes drugs such as pharmaceutical agent(s) or radioactive agent(s) for delivery to an implant site. The sheath includes a main body of a generally tubular shape, and may include mounting means for attaching same to the stent. The device may have a slit therein, and may comprise a helical coil, a cylinder or any other suitable shape or design which fits a particular stent. The sheath may include a coating or coatings thereon containing drugs, surgical adhesives or a combination thereof.



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Description

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DRUG DELIVERY DEVICE FOR STENT**BACKGROUND OF THE INVENTION**

This invention relates to a device for providing mechanical support to a vessel lumen of a living being. This invention also relates to the delivery of materials which prevent restenosis of a vessel.

A variety of medical situations requires the use of a mechanism to expand and support a constricted vessel and to maintain an open passageway through the vessel. A few examples of such situations following angioplasty include holding a dissection in place, preventing closure during spasm, and preventing acute closure due to thrombosis. In these situations, devices, commonly known as stents, are useful to maintain the patency of body passages, to prevent stenosis of a dilated vessel, to eliminate the danger of occlusion caused by "flaps" resulting from intimal tears that may be associated with angioplasty, or to hold two ends of a vessel in place.

Stents are generally tubular in configuration, open ended and are expandable between a generally unexpanded insertion diameter and an expanded implantation diameter. Stents are commonly placed or implanted by a mechanical transluminal procedure.

Specifically, U.S. Patent 4,733,665 to Palmaz discloses a number of stent configurations for implantation with the aid of a catheter. U.S. Patent 5,019,090 to Pinchuk discloses a generally cylindrical stent and technique for implanting it using a deflated balloon catheter to position the stent. U.S. Patents 4,503,569 to Dotter and 4,512,338 to Balko et al. disclose a spring stent and a shape memory alloy stent. There are also self-expanding stents such as those described in U.S. Patents 4,732,152 to Wallsten et al. and 4,848,343 to Wallsten et al. All of these patents are hereby incorporated by reference.

Stents have been made using materials of varied composition and conformation. McGreevy et al U.S. Patents 4,690,684 and 4,770,176 describe a meltable stent that is inserted into the interior of the ends of a blood vessel during anastomosis. Anastomosis refers to the surgical or physical connection of two tubular structures, such as veins or arteries. The stent is made of blood plasma, which is biologically compatible with the living being and which melts rapidly in response to heat.

Fischell et al., in U.S. Patent 4,768,507 describe an intravascular stent which is an unrestrained coil spring having an outside diameter of 2 to 12 millimeters and a length of 5 to 25 millimeters. The materials of construction are stainless steel, and a

5 titanium alloy. Decreased thrombogenicity is achievable by coating the outside of the coil with a non-thrombogenic material such as ULTI carbon.

10 Leeven et al., in U.S. Patent 4,820,298 describe a stent having a flexible tubular body made from a thermal plastic to the form of a helix. Polyester and
5 polycarbonate copolymers are selected as particularly desirable materials.

15 Wolff et al., in U.S. Patent 4,830,003 describe a stent made from wires formed into a cylinder. The wires are made of a biocompatible metal. Biocompatible metals include 300 series stainless steels such as 316 LSS, as well as platinum and platinum-iridium alloys, cobalt-chromium alloys such as MP35N, and unalloyed titanium.

20 Wiktor in U.S. Patent 4,886,062 describes a stent made from low memory metal such as a copper alloy, titanium, or gold. The stent is preformed into a two-dimensional zig-zag form creating a flat expandable band.

25 Gianturco in U.S. Patent 4,907,336 describes a wire stent having a cylindrical shape that results from an expandable serpentine configuration. Malleable
15 materials of construction are preferably included from the group of annealed stainless steels, tungsten and platinum.

30 Goldberg et al, in Canadian Application 2,025,626, describes a bio-degradable infusion stent used to treat ureteral obstructions. The application describes an extruded material of construction made of epsilon-caprolactone (15-25% w/w of
20 terpolymer composition); glycoside (5-50% w/w) and L(-)lactide (45-85% w/w). This material was described as having a minimum tensile strength of at least 500 pounds per square inch, preferably 650 psi; elongation of greater than 10%, preferably greater than 100%; and Shore A hardness equal to 50-100%, preferably 75-95%. The Goldberg et al
35 patent application describes a method for incorporating radiopaque materials such as
40 25 barium sulfate into the polymer in amounts ranging from 5-30%. The mechanism of biodegradation is described as hydrolysis resulting in degradable products excreted in urine or reabsorbed into tissues. The duration of functional life of the stent is estimated at about
45 3-7 weeks.

50 Wilcoff in U.S. Patent 4,990,155 describes a plastic stent having an
30 inherently expandable coil conformation. The "inherency" results from an elastic memory conferred by electron beam radiation imparting cross-linkages that provide an inherent tendency to return to a given diameter after any distortion. Materials of construction

5 include high density polyethylene. Optionally, this material is compounded with an anti-coagulant and/or an x-ray opaque material such as bismuth-sub-carbonate.

10 Sigwart, Canadian Patent Application 2,008,312, describes a stent made from a malleable flat sheet having a reticulated pattern. The reticulated pattern includes
5 non-deformable squares or diamonds. The stent is made by rolling the sheet and locking the sheet into a spiral having a small diameter. The sheet is locked into a spiral by a tie interwoven into the reticulated pattern. Once inserted into the lumen of a vessel, the spiral
15 is expanded and held in place by flaps integrated into the outer body of the stent.

Shockley et al., in U.S. Patent 4,994,033, describe a drug delivery dilatation
10 catheter having three flexible, plastic tubes concentrically arranged relative to each other. The outermost sleeve of this catheter contains microholes for drug delivery. These microholes are made with a laser beam. Drugs that can be delivered by this system include aspirin, persantin, heparin, and prostaglandins. Drugs are delivered when externally
20 applied pressure causes the innermost sleeve to balloon out. The drug is then forced
25 through the microholes to spray and to treat a lesion.

There are also stents which deliver agents or drugs to blood passing through the vein or artery that are generally beneficial to the recipient. In addition, stents can deliver drugs or biologically active agents at a controlled rate to blood passing through the vessel lumen as well as to the vessel wall. Silvestrini in U.S. Patent 5,234,456 describes
30 a hydrophilic stent comprising a wall structure where at least a portion thereof is a hollow wall in which a hydrophilic material for drug delivery is placed. U.S. Patent 5,443,458 to Eury et al., is directed to a multilayer laminated resorbable stent having a structural layer and additional layers stated to release drugs at predictable rates. Froix in U.S. 5,258,020 describes a self-restrained stent with an elastic memory, the stent optionally being
40 formulated to provide for drug administration.

It is known that when stents are expanded to their implantation diameter the ends of the stent may press into the vessel or cavity walls, especially the distal end of the stent. The sharp or pointed edges and ends of some stents may then damage the walls.
45 Once damage has occurred, there is a likelihood that restenosis will occur at these points
30 where the stents ends and edges have penetrated or pressed against the walls.

Restenosis occurs in a number of cases where a stent has been used. Tearing
50 of the wall of the passage or injury of the endothelial cell layer are possible causes of the

5 restenosis. The torn wall or flap usually is the source of the blockage. When the wall is
torn, a flap of tissue is created, which falls into the passage and blocks it. It is then
10 necessary to perform another procedure to remove the blockage and generally, another
stent is needed to open the vessel or other passage. Metal stents are known to cause 10%
5 to 30% or more restenosis in application.

Therefore, it desirable to utilize a stent which reduces the chances of a
15 damaged vessel wall or body passage which leads to further problems and further necessary
procedures. However, current stents are not designed to reduce the occurrence of cutting
of vascular passages or the like.

20 U.S. Patent Application No. 09/072,944, incorporated herein by reference,
is directed to a stent having at least one smooth end. The stent may include a coating or
coatings on one or both end portions to provide a smooth finish to reduce possible damage
to body passages when the stent is deployed and delivered. The stent may also contain
25 drugs or surgical adhesives or a combination thereof in or on the coated portion of the stent.
15 The stent may also be of the type where the materials of the stent may be treated to have
a smooth flexible end or ends. The stent may also be of a configuration such that at least
one end is more flexible than the middle portion of the stent.

30 U.S. Patent Application No. 08/874,190, incorporated herein by reference,
discloses a polymeric layered stent characterized in that it includes a multilayered material
20 comprised of an inner polymer layer and an overlying outer polymer layer. The self-
expanding or balloon expandable stent disclosed therein is provided in two forms, one
35 including inner and outer polymeric layers, and another comprising a prior art stent
provided with polymeric layer(s) coated thereon.

40 While U.S. Applications 09/072,944 and 08/874,190 are directed in part to
25 this need, there still exists a need for a means for delivering drugs or biologically active
agents which assist in preventing restenosis, which can be easily mounted on an existing
stent prior to implantation.

45 SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention is to provide a polymeric
30 device adapted for mounting onto a stent. The device of polymeric material may comprise
a sheath or sleeve that is cylindrical, a helical coil, or any other suitable shape or design
50 which fits a particular stent. The stent may be metallic or non-metallic, or alternatively a

5 combination of metallic and non-metallic materials. An example of a preferred stent for
use with the device of the present invention is the NIR stent, set forth in U.S. Patent
5,733,303, incorporated herein by reference. In addition, the device may be used with a
10 stent as set forth in U.S. Application No. 08/874,190, incorporated herein by reference.

5 The device may be of a biocompatible material and may be either
biodegradable or non-biodegradable. The device may also be water soluble. It may contain
pharmaceutical agent(s) or radioactive agent(s). The device is adapted for mounting onto
15 a stent prior to use for insertion into a lumen of a vessel in a living being, and may be
expanded with the stent. The device is optionally biodegradable, and may be made from
10 at least one biodegradable material that is also biocompatible and includes a drug which is
released into the lumen of the vessel at a rate controlled by the rate of degradation of the
20 biodegradable material.

Generally, any prior art stent may be improved by providing it with the
device of the present invention. The use of this inventive device with an existing stent
25 provides a simple method for reducing restenosis.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is an enlarged perspective view of a device according to the present
30 invention;

Figures 2a and 2b are perspective views of an alternative embodiment of the
20 device of the present invention;

Figure 3 is a perspective view of an alternative embodiment of the device of
35 the present invention;

Figure 4 is a perspective view of an alternative embodiment of the device
of the present invention;

40 Figure 5 is a cross section taken along the line 5-5 of Figure 4;

Figure 6 is a perspective view of an alternative embodiment of a device
according to the present invention;

45 Figure 7 is a cross section taken along line 7-7 of Figure 6;

Figure 8 is a perspective view of an alternative embodiment of a device
30 according to the present invention;

Figure 9 is a fragmentary perspective view of the sheath as shown in Figure
50 8 mounted on a stent;

Figure 10 is a fragmentary perspective view as in Figure 9 showing the stent and sheath after expansion of the stent; and

Figure 11 is a fragmentary side elevational view with parts broken away of the stent with the sheath of the present invention in an implanted site.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is a polymeric device adapted for mounting onto a stent. Referring to Figures 1-4, the device may be a sheath as shown generally at 10. Sheath 10 has a proximal end 12, a distal end 14, an interior surface 16 and an exterior surface 18.

As shown at Figures 2a, 2b and 3, sheath 10 may have a slit 15 therein extending from proximal end 12 to distal end 14. As shown at Figure 2a, slit 15 is a longitudinal slit 15a. Figure 2b shows the same sheath in a compressed configuration it may take on prior to being mounted on a stent. Alternatively, slit 15 may be a helical slit 15b, as shown at Figure 3.

Referring to Figure 4, sheath 10 may be provided with perforations 17 therethrough. In addition, sheath 10 may comprise multiple layers, for example as shown in cross section at Figure 5 having two layers. Alternatively, sheath 10 may comprise a plurality of layers. Referring to Figures 6-7, sheath 10 may be shaped like a spring, which spring may optionally be formed from a tubular member, as exemplified by the cross section at Figure 7.

Referring now to Figures 8-10, a sheath comprising a helical coil is shown. Figure 8 is a perspective view of sheath 10. At Figure 9, a partial section view of sheath 10 mounted on a stent 20 is shown prior to implantation and expansion. Stent 20 includes a generally tubular main body 21, a proximal end 22 (not shown in this view), a distal end 24 (not shown in this view), an interior surface 26 and an exterior surface 28. Prior to implantation, sheath 10 is mounted on stent 20 such that the exterior surface 28 of main body 21 faces the interior surface 16 of sheath 10.

In use, sheath 10 is placed on the outer surface 24 of stent 20 prior to implantation thereof. Sheath 10 may be held on stent 20 by any suitable means including compressive force, glue, a protective sheath, socks or the like.

The compressive force may be supplied by the sheath itself, the stent or both. The glue is preferably a biocompatible glue such as fibrin, collagen or gelatin. Any

appropriate bioadhesive may be used. For example, the following bioadhesives may be used singly or in combination:

cyanoacrylate: ethyl cyanoacrylate, butyl cyanoacrylate, octyl cyanoacrylate, hexyl cyanoacrylate;

fibrin glue: fibrinogen/thrombin/Factor XIII/calcium as catalyst
gelatin-resorcinol-formol (GRF) glue: formed from gelatin, resorcinol and water in the presence of formaldehyde, glutaraldehyde and heat (45°C);

mussel adhesive protein, prolamine gel and transforming growth factor beta(TGF-B);

polyacrylic acid, modified hydrocellulose, hydroxypropylmethyl cellulose, hydroxypropylcellulose, carboxymethyl cellulose, sodium alginate, gelatin, pectin, polyvinylpyrrolidone, polyethylene glycol, aldehyde relative multifunctional chemicals, polyallylsaccharose, and polypeptides.

A protective sheath may also be used to secure sheath 10 to stent 20. A sheath or sheaths as disclosed in U.S. Application Nos. 08/812,351 and 09/034,434, incorporated herein by reference, may be used, but would be retained over sheath 10 in use.

At least one sock covering a portion of sheath 10 over stent 20 may also be used. Such a retaining device as is disclosed in U.S. Application No. 08/917,027, incorporated herein by reference, may be used.

One use of the sheath of the present invention is to allow physicians to add it to any stent and delivery system they already have. The sheath may therefore be provided as a stand alone device.

Stent 20 with sheath 10 mounted thereto is positioned at the inner surface wall 34 of the vessel 32 by radially compressing the stent with sheath to a tubular diameter less than the diameter of the vessel 32 and moving stent 20 to a desired site within vessel 32. Stent 20 is implanted in the known manner depending upon its type. For example, a self expanding stent would be released from compression so that the stent can radially spring out to abut against the inner surface wall 34 of vessel 32. The stent may also be of the balloon expandable type. In any case, sheath 10 is adapted for mounting onto stent 20 and expansion therewith. Figure 10 shows sheath 10 after expansion of stent 20.

At Figure 11, sheath 10 and stent 20 are shown in an implanted site, in the lumen 30 of a tubular vessel 32 in a body. Upon implantation, the exterior surface 18 of

5 sheath 10 faces an inner surface wall 34 of the vessel 32. Stent 20 provides mechanical support to tubular vessel 32 in a living being. The stent strengthens the area of vessel 32 in which it is implanted. Sheath 10 releases a pharmaceutical agent or radioactive agent
10 into lumen 30 of tubular vessel 32. The rate of release may vary.

5 The present invention may be used with any stent. Such a stent may range from 1 millimeter in diameter to 50 millimeters in diameter and from 1 millimeter in length to 50 millimeters in length. The size of the stent is dictated by the lumen of the vessel to which the stent is placed. Tubular main body 21 suitably has a length of up to approximately 5 centimeters.

15 Sheath 10 may be of any size suitable for use with a stent being implanted.
20 Many suitable materials may be used to form the sheath 10 of the present invention. For example, hydrophilic polymers, copolymers (block or graft) or their cross-linked versions (e.g. hydrogels), may be used, the polymers including poly(hydroxyethyl methacrylate) and derivatives; poly(vinyl alcohol); polyethylene oxide; poly(propylene
25 oxide); polyacrylamides; polyacrylic acid; polymethacrylic acid; poly(N-vinyl-2-pyrrolidone); hydrophilic polyurethanes; poly(amino acid); water soluble cellulosic polymers (sodium carboxymethyl cellulose, hydroxyethyl cellulose, for example);
30 collagens; carrageenan; alginate; starch; dextrin; and gelatins.

The device of the present invention may be made of biodegradable polymers
35 including poly(lactide); poly(glycolide); polydioxanone(PDS); polycaprolactone; polyhydroxybutyrate(PHBT); poly(phosphazene); poly(phosphate ester); poly(lactide-co-glycolide); poly(glycolide-co-trimethylene carbonate); poly(glycolide-co-caprolactone); polyanhydrides; collagen or other connective proteins or natural materials, hyaluronic acid, adhesive proteins, co-polymers of these materials as well as composites or combinations
40 thereof and combinations of other biodegradable polymers.

In addition, the device of the present invention may be made of biodegradable materials that are also biocompatible. By biodegradable is meant that a material will undergo breakdown or decomposition into harmless compounds as part of a normal biological process. The device may also include bioactive agents which permit
45 endothelial cells to grow on the device and the stent. It is believed that the endothelial cell growth will encapsulate particles of the stent during biodegradation that would otherwise
50 come loose and form emboli in the blood stream.

5 Suitable biodegradable materials for the device of the present invention include polylactic acid, polyglycolic acid, collagen or other connective proteins or natural materials, polycaprolactone, hyaluronic acid, adhesive proteins, co-polymers of these materials as well as composites and combinations thereof, and combinations of other 10 biodegradable polymers. Biodegradable glass or bioactive glass is also a suitable biodegradable material for use in the present invention. Preferably the materials have been accepted by the U.S. Food and Drug Administration. 15

One advantage of using a variety of biodegradable materials within the sheath is control of degradation. Biodegradable materials degrade at different rates, ranging 10 from days or weeks to several years. Consequently, the presence of different biodegradable materials in the stent permits the sheath to degrade in a predictable manner. The device may further be coated with a biodegradable film layer. 20

Where sheath 10 is of a biodegradable material, the rate of release of the pharmaceutical agent or radioactive agent will be controlled by the rate of degradation of 25 the biodegradable materials. 15

Further, the device of the present invention may be made of nonbiodegradable biocompatible materials such as polytetrafluoroethylene(PTFE); polyurethanes; polyamides; polyesters; polyethers; polyketones; polyether ester elastomers; polyether amide elastomers; polyacrylate-based elastomers; polyethylene; and 20 polypropylene. 30

These lists are exemplary only. Any appropriate material may be used. 35

The sheath of the present invention includes pharmaceutical agent(s) and/or radioactive agent(s) or other biologically active materials. Where the sheath is biodegradable, these drugs, pharmaceutical agents, radioactive agents or biologically active 40 materials are contained within the biodegradable materials of which the stent is composed. As the sheath biodegrades, drugs are released into the surrounding tissue or to the bloodstream. Thus, the rate of drug release is controlled by the rate of degradation of the biodegradable materials. A material that degrades rapidly will release the drug faster than 45 a material that degrades slowly. 25

Drugs are incorporated into the biodegradable sheath using techniques known in the art. The techniques include simple mixing or solubilizing with polymer 50 55

5 solutions, dispersing into the biodegradable polymer during the formation of the sheath, or coating onto an already formed sheath.

10 Where the sheath has a film added thereto, drugs can be incorporated into the film by methods such as melting or solvation. Alternatively, biologically active agents
5 are incorporated into the film layer by entrapment between such layer and the surface of biodegradable material sandwiched together, thereby further promoting release of the drugs or agents in a controllable manner.

15 The drugs or other biologically active materials incorporated into the sheath of the present invention perform a variety of functions. The functions include but are not
10 limited to an anti-clotting or anti-platelet function and preventing smooth muscle cell growth on the inner surface of the vessel to reduce the chance of in-stent restenosis. The drugs include but are not limited to drugs that inhibit or control the formation of thrombus or thrombolytics such as heparin or heparin fragments, aspirin, coumadin, tissue plasminogen activator (TPA), urokinase, hirudin, and streptokinase, antiproliferatives
25 (methotrexate, cisplatin, 5-fluorouracil, Taxol, Adriamycin, and the like) antioxidants (ascorbic acid, carotene, B, vitamin E, and the like), antimetabolites, thromboxane inhibitors, non-steroidal and steroidal antiinflammatory drugs, Beta and Calcium channel blockers, genetic materials including DNA and RNA fragments, and complete expression
30 genes, carbohydrates, and proteins including but not limited to antibodies (monoclonal and polyclonal) lymphokines and growth factors, prostaglandins, and leukotrienes. The sheath material may also incorporate bioactive materials such as fibronectin, laminin, elastin, collagen, and integrins. Fibronectin, for example, promotes adherence of the sheath to the
35 tissue of the vessel 32.

40 In one specific example of a biodegradable material incorporating drugs, a poly-L-lactide having an intrinsic viscosity of 2.3 dl/g is used to form monofilament fibers
25 using a spin or melt spinning process. Five percent aspirin or 5% heparin was incorporated into the melt of the poly-L-lactide prior to fiber formation. The fibers formed had a diameter of approximately 0.5 millimeters. The monofilaments were then stretched under
45 temperatures ranging from 50° C to 200° C to orient the fiber. The temperature employed depends upon the kind of material used to make the fiber. The final diameter of the
30 oriented fiber falls within a range of 0.1 to 0.3 millimeters. Similar processing was used to incorporate 5% aspirin or 5% heparin into poly-L-lactide and polyglycolide.

5 The device of the present invention may also include bioadhesives to be delivered to the site where the stent is needed. It is known that bioadhesives can be used to repair tissue walls. It is therefore desirable to utilize a polymer to deliver a bioadhesive to the stent implantation location. In this manner, a potential problem could be averted by the presence of the bioadhesive in the case of a tear or dissection.

10 Just as the use of a variety of biodegradable materials facilitates a controlled degradation of a biodegradable sheath according to the present invention, so similarly does the incorporation of a variety of drugs into the biodegradable materials facilitate control of drug release to perform a variety of functions. For instance, drugs released from the outer surface as the outer surface degrades facilitate adherence of the sheath to the inner surface wall 34 of the vessel 32. Drugs released from fibers perform a variety of functions, ranging from promoting cell growth to altering the blood clotting mechanisms, depending upon what drug released. In one embodiment, drugs released from the sheath as it degrades may temper platelet function in blood flowing through lumen.

15 The device of the present invention may also be used as a drug delivery system to prevent restenosis or for other treatment. The drugs may include radioactive materials to irradiate and prohibit smooth muscle cell growth. Angioplasty and stent deployment may cause injury of the endothelial cell layer of blood vessels, causing smooth muscle cell proliferation, leading to restenosis. By accelerated endothelialization on the inner wall surface of vessels will prevent or prohibit the smooth muscle growth. To stimulate endothelialization without provoking smooth muscle cell proliferation, specific growth factors may be included and delivered. Growth factors include vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF β), insulin growth factor-1 (IGF-1), platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), etc.

20 All such materials are referred to herein generally as "drugs" or therapeutics. These drugs may be dispersed in the matrix of the polymeric material.

25 For carrying drugs, a gel-like material may be used. The sleeve may be comprised of such a material, or it may be applied over the sleeve as a coating. There are several ways to apply drugs to such materials. The first way is to mix the drug with the materials, then form a sleeve therefrom. Alternatively the mixture may coated onto a sleeve. The gel-like materials can be cast as film or sheet with drug together, then formed into a sleeve or laminated to a sleeve.

5 Another way is to form a sleeve from a gel-like material without a drug, or
to coat or laminate a polymeric sleeve with a gel-like material without the drug. The sleeve
is made, and then sterilized. Due to the gel-like nature, the sleeve can then be inserted into
10 a drug solution. The drug will be absorbed into/onto the gel.

5 The resulting drug-carrying sleeve can then be mounted to a stent and
delivered into the body. The drug will then be released.

15 In one embodiment of the invention, the sleeve may be made of
polyethylene oxide containing Taxol or coated with such a material. Other materials that
may be used are copolymers such as PGA/PLA, PEO/PLA or the like containing a drug
10 such as Taxol or heparin.

20 Preferred gel-like materials for use as a drug delivery sleeve or coating for
a stent when drug delivery is desired are polyethylene oxide, polyvinyl pyrrolidone,
polyacrylates, and their blends or copolymers or lightly cross linked forms. Polyethylene
glycol block copolymer with polylactides or other polyesters are examples. Hydrophilic
25 polyurethane, poly(maleic anhydride-alt-ethylene) and their derivatives are examples.
Other materials are polysaccharides and their derivatives. There are also sodium alginate,
karaya gum, gelatin, guar gum, agar, algin carrageenans, pectin, locust bean gums, xanthan,
30 starch-based gums, hydroxy alkyl and ethyl ethers of cellulose, sodium carboxymethyl
cellulose. Some of the materials will be heated, then cooled, then a gel is formed. Some
20 of the above are food gels. Some of them are bioadhesives.

35 Any drugs may be used, singly or in combination. For example, the drugs
can be an anticoagulant, e.g. aspirin, ticlopidine, an RGD peptide-containing compound,
heparin, antithrombin compounds, platelet receptor antagonists, antibodies, urokinase,
prostaglandin inhibitors, platelet inhibitors, or antiplatelet peptide. The drug can be an
40 25 inhibitor of vascular cell growth, DNA, RNA, cholesterol-lowering agents, vasodilating
agents. The drug can be any drug such as Taxol, 5-fluorouracil, Beta-Estradiol, Tranilast,
Trepidil, Probucol, Angiopeptin or any combination of them.

45 Since there are many drugs and many polymers, the sleeve can have multiple
layers of different polymers with the same or different drugs. For example, the sleeve can
30 have two layers of the same polymer with one layer with drug and another layer without
drugs. The sleeve may have two layers of the same polymer with two different drugs as
50 another example.

5 In particular, various combinations of a cycling sinase inhibitor identified
as p21 and the vascular endothelial growth factor identified as VEGF, an endothelial
10 nitrogen, may preferably be included in and dispensed from the sleeve or coating provided
thereon.

5 Incorporation of drugs and growth factors into the sleeve material or coating
thereof can also be performed by several other methods, including the solvent method,
15 melting method, soaking method and spraying method. If both polymer and drug have a
cosolvent, a solution case will be an easy way to provide the polymer matrix loaded with
the drug or growth factor. If the polymer can be melted at low temperature and the drug
10 or growth factor tolerates heating, a melting method can be used to mix the drug or growth
factor into the polymer matrix. Also, a polymer-drug solution or suspension solution can
20 be used for coating to provide a layer containing the drug or growth factor.

In another embodiment of the invention the sleeve may be coated with a film
25 of bioadhesive. Bioadhesives glue the tissue together. Using a bioadhesive for the coating
serves two purposes. If a tear has occurred prior to or during delivery of the stent on which
15 the sleeve is mounted, the tissue can be repaired. In this manner, blood flow will be
maintained in a vessel, for example. The bioadhesive may or may not also have drugs
loaded for delivery. Dissection, cutting or tearing occurs in some stent delivery and PTCA
30 procedures. Bioadhesives or surgical adhesives may be used to repair the passage wall.
However, these tears or cuts are not necessarily discovered immediately. In those cases,
20 a further medical procedure must be undertaken to repair the wall. The need for such an
additional medical procedure may be eliminated where a bioadhesive is included as a
coating on the sleeve mounted to the stent which is deployed in place, as the bioadhesive
35 will repair damage to the vessel wall. The bioadhesive is chosen as the coating for the
sleeve, or is used in addition to a coating on the sleeve and is applied in a known manner
40 to the sleeve. The end or edge, side, outside and/or inside of the sleeve may utilize the
bioadhesive.

45 Any appropriate bioadhesive may be used. For example, the following
bioadhesives may be used singly or in combination:

30 cyanoacrylate: ethyl cyanoacrylate, butyl cyanoacrylate, octyl cyanoacrylate,
hexyl cyanoacrylate;

50 fibrin glue: fibrinogen/thrombin/Factor XIII/calcium as catalyst

5 gelatin-resorcinol-formol (GRF) glue: formed from gelatin, resorcinol and water in the presence of formaldehyde, glutaraldehyde and heat (45°C);

10 mussel adhesive protein, prolamine gel and transforming growth factor beta(TGF-B);

5 polyacrylic acid, modified hydrocellulose, hydroxypropylmethyl cellulose, hydroxypropylcellulose, carboxymethyl cellulose, sodium alginate, gelatin, pectin, polyvinylpylindone, polyethylene glycol, aldehyde relative multifunctional chemicals, polyallylsaccharose, and polypeptides.

15 Suitable materials for the device of the present invention and suitable drugs
10 to be delivered thereby are also set forth in U.S. Application No. 08/874,190.

20 Although the present invention has been described with reference to preferred embodiments, workers skilled in the art will recognize that changes may be made in form and detail without departing from the spirit and scope of the invention.

25 The above Examples and disclosure are intended to be illustrative and not
15 exhaustive. These examples and description will suggest many variations and alternatives to one of ordinary skill in this art. All these alternatives and variations are intended to be included within the scope of the attached claims. Those familiar with the art may recognize other equivalents to the specific embodiments described herein which equivalents are also intended to be encompassed by the claims attached hereto.

20 F:\WPWORK\WEA\8471-APP.831

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Claims

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WHAT IS CLAIMED IS:

What is claimed is:

1. An implantable intraluminal apparatus comprising in combination:
an expandable intraluminal stent comprising a main body portion having a first end
portion, a second end portion, a middle portion, an exterior surface and an interior flow
passage defined therethrough; and
a sheath constructed and arranged for mounting on the stent for delivery of drugs
to an implanted site, said sheath comprising a biocompatible polymeric material and a drug
carried thereby.
2. The apparatus of claim 1 wherein the sheath comprises polyurethane.
3. The apparatus of claim 1 wherein the sheath comprises polytetrafluoroethylene.
4. The apparatus of claim 1 wherein the sheath comprises a gel-like material.
5. The apparatus of claim 1 wherein the sheath comprises a cellulose polymer.
6. The apparatus of claim 1 wherein the sheath comprises a biodegradable polymer.
7. The apparatus of claim 1 wherein the sheath comprises poly(N-vinyl-2-pyrrolidone).
8. The apparatus of claim 1 wherein the sheath comprises polyethylene oxide.
9. The apparatus of claim 1 wherein the drug is selected from the group consisting of
pharmaceutical agents, radioactive agents, bioactive agents and combinations thereof.
10. The apparatus of claim 1 wherein the drug is selected from the group consisting of
TAXOL, vascular endothelial growth factor, heparin, 5-fluorouracil, beta-estradiol,
tranilast, trapidil, probucol, and angiopeptin.
12. The apparatus of claim 1 wherein the sheath is cylindrical.
13. The apparatus of claim 1 wherein the sheath further comprises a proximal end, a
distal end and a slit extending from the proximal end to the distal end.
14. The apparatus of claim 13 wherein the slit is a longitudinal slit.
15. The apparatus of claim 13 wherein the slit is helical.
16. The apparatus of claim 1 wherein the sheath is a helical coil.
17. The apparatus of claim 1 wherein the sheath comprises a plurality of layers.
18. The apparatus of claim 17 wherein the plurality of layers is comprised of the same
material.
19. The apparatus of claim 17 wherein the plurality of layers is comprised of different
materials.

- 5 20. The apparatus of claim 17 wherein at least one of the layers includes a drug.
21. The apparatus of claim 1 wherein the sheath further comprises an inner surface, an
10 outer surface, and a coating covering at least a portion of the outer surface thereof.
- 5 22. The apparatus of claim 21 wherein the coating comprises a biocompatible polymer.
23. The apparatus of claim 21 wherein the coating comprises polyethylene oxide.
24. The apparatus of claim 21 wherein the coating comprises polyurethane.
- 15 25. The apparatus of claim 21 wherein the coating comprises a gel-like material.
26. The apparatus of claim 21 wherein the drug is carried by the coating.
- 10 27. The apparatus of claim 21 wherein the coating includes a bioadhesive.
- 20 28. The apparatus of claim 27 wherein the bioadhesive is selected from the group
 consisting of cyanoacrylate, fibrin glue, gelatin-resorcinol-formol glue.
29. The apparatus of claim 21 wherein the coating comprises a plurality of layers.
- 25 30. The apparatus of claim 29 wherein the plurality of layers is comprised of the same
15 coating material.
31. The apparatus of claim 29 wherein the plurality of layers is comprised of different
 coating materials.
- 30 32. The apparatus of claim 29 wherein at least one of the layers includes a drug.
33. An implantable intraluminal apparatus comprising:
20 a sheath constructed and arranged for mounting on a stent for delivery of drugs to
35 an implanted site, said sheath comprising a biocompatible polymeric material and a drug
 carried thereby.
34. A sheath constructed and arranged for mounting on a stent for delivery of drugs to
40 an implanted site, said sheath comprising a biocompatible polymeric material and a drug
25 carried thereby.
35. A sheath for an implantable intraluminal apparatus for delivery of a stent, the sheath
45 constructed and arranged for mounting on a stent for delivery of drugs to an implanted site,
 said sheath comprising a biocompatible polymeric material and a drug carried thereby.
- 30 36. A sheath for being delivery into the body with a stent, the sheath constructed and
 arranged for mounting on a stent for delivery of drugs to an implanted site, said sheath
 comprising a biocompatible polymeric material and a drug carried thereby.
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37. A drug delivery sheath for delivering drugs within the body, the sheath constructed and arranged for being associated with a stent for delivery of drugs to an implanted site, said sheath comprising a biocompatible polymeric material and a drug carried thereby.

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38. A sheath constructed and arranged for being introduced within the body for delivery of drugs to an implanted site, said sheath comprising a biocompatible polymeric material and a drug carried thereby.

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Fig. 1

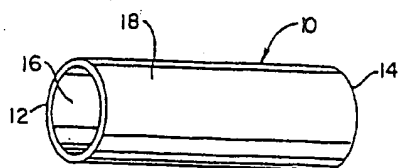


Fig. 2a

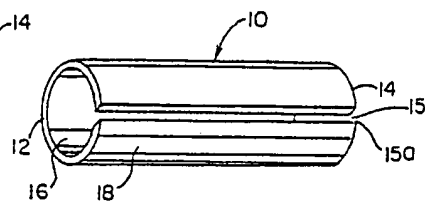


Fig. 3

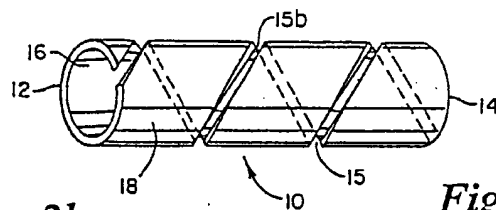


Fig. 7



Fig. 2b

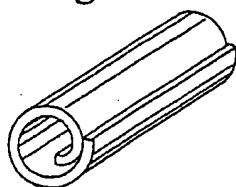


Fig. 4

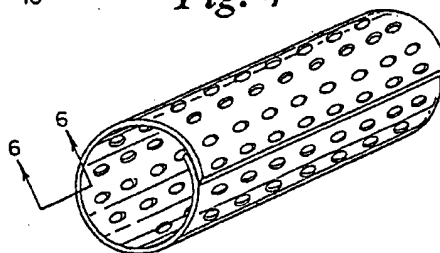


Fig. 5

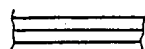


Fig. 6

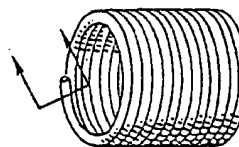


Fig. 8

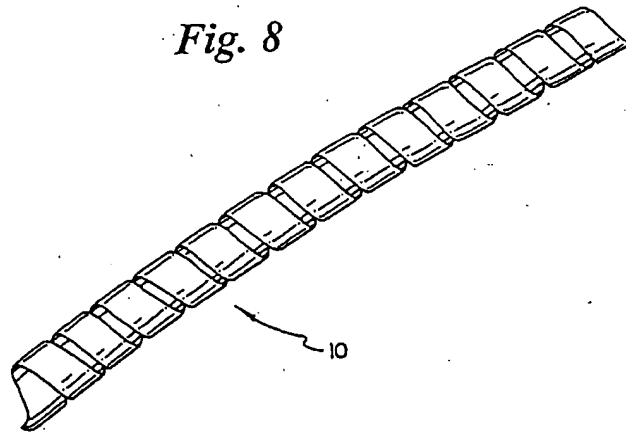


Fig. 9

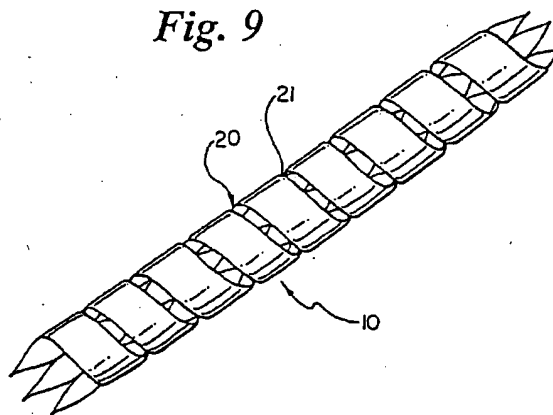


Fig. 10

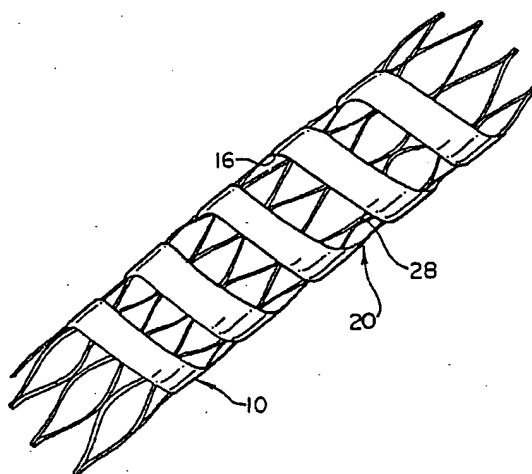
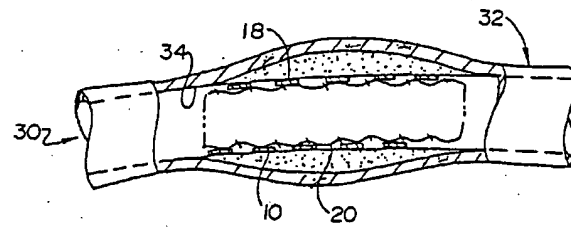


Fig. 11

INTERNATIONAL SEARCH REPORT

Int. l. Application No
PCT/US 99/19697

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61L31/08 A61L31/16 A61L31/18 A61K51/12 A61F2/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61L A61K A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 383 928 A (SCOTT NEAL A ET AL) 24 January 1995 (1995-01-24) claims; figure 3	1-38
X	EP 0 716 836 A (ADVANCED CARDIOVASCULAR SYSTEM) 19 June 1996 (1996-06-19) claims; figures	1-38
X	EP 0 712 615 A (ADVANCED CARDIOVASCULAR SYSTEM) 22 May 1996 (1996-05-22) claims	1-38
X	EP 0 604 022 A (ADVANCED CARDIOVASCULAR SYSTEM) 29 June 1994 (1994-06-29) claims	1, 6, 9, 11, 17-22, 26, 29-38

☒ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

18 January 2000

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

International Application No

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: A61L 31/10	A1	(11) International Publication Number: WO 00/02599 (43) International Publication Date: 20 January 2000 (20.01.2000)
(21) International Application Number: PCT/IL99/00376 (22) International Filing Date: 08 July 1999 (08.07.1999) (30) Priority Data: 09/112,125 08 July 1998 (08.07.1998) US (60) Parent Application or Grant ADVANCED BIOCOMPATIBLE COATINGS INC. [/]; (). BINDERMAN, Itzhak [/]; (). BINDERMAN, Itzhak [/]; (). WOLFF, BREGMAN AND GOLLER ; ().		Published
(54) Title: BIOCOMPATIBLE METALLIC STENTS WITH HYDROXY METHACRYLATE COATING (54) Titre: STENT METALLIQUE BIOCOMPATIBLE A REVETEMENT D'HYDROXYMETHACRYLATE (57) Abstract <p>The invention provides a hemo-compatible, restenosis-inhibiting metallic stent, comprising a coating of a poly-hydroxy methacrylate derivate selected from the group consisting of poly-hydroxyethylmethacrylate (PHEMA), poly (hydroxyethoxyethyl methacrylate) (PHEEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly (methoxyethyl methacrylate) (PMEMA), poly (methoxyethoxyethyl methacrylate) PMEEMA, poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), poly (ethylene glycol dimethacrylate) (PEGDMA), and mixtures thereof.</p> (57) Abrégé <p>L'invention concerne un stent métallique hémocompatible, inhibant la resténose, comprenant un revêtement de polyhydroxyméthacrylate sélectionné dans le groupe comprenant le polyhydroxyéthyl méthacrylate (PHEMA), le poly(hydroxyéthoxyéthyl méthacrylate) (PHEEMA), le poly(hydroxydiéthoxyéthyl méthacrylate) (PHDEEMA), le poly(méthoxyéthyl méthacrylate) (PMEMA), le poly(méthoxyéthoxyéthyl méthacrylate) (PMEEMA), le poly(méthoxydiéthoxyéthyl méthacrylate) (PMDEEMA), le poly(éthylèneglycol diméthacrylate) (PEGDMA), ainsi que des mélanges de ces composés.</p>		

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61L 31/10		A1	(11) International Publication Number: WO 00/02599 (43) International Publication Date: 20 January 2000 (20.01.00)
(21) International Application Number: PCT/IL99/00376 (22) International Filing Date: 8 July 1999 (08.07.99) (30) Priority Data: 09/112,125 8 July 1998 (08.07.98) US (71) Applicant (for all designated States except US): ADVANCED BIOCOMPATIBLE COATINGS INC. [US/US]; 1313 N. Market Street, Wilmington, DE 19801-1151 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): BINDERMAN, Itzhak [IL/IL]; Fievel Street 13, 62995 Tel-Aviv (IL). (74) Agent: WOLFF, BREGMAN AND GOLLER; P.O. Box 1352, 91013 Jerusalem (IL).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW. ARIPO patent (GH, GM, KE, LS, MW, SD, SI, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(54) Title: BIOCOMPATIBLE METALLIC STENTS WITH HYDROXY METHACRYLATE COATING			
(57) Abstract <p>The invention provides a hemo-compatible, restenosis-inhibiting metallic stent, comprising a coating of a poly-hydroxy methacrylate derivate selected from the group consisting of poly-hydroxyethylmethacrylate (PHEMA), poly (hydroxyethoxyethyl methacrylate) (PHEEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly (methoxyethyl methacrylate) (PMEEMA), poly (methoxyethoxyethyl methacrylate) (PMEEMA), poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), poly (ethylene glycol dimethacrylate) (PEGDMA), and mixtures thereof.</p>			

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Description

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BIOCOMPATIBLE METALLIC STENTS WITH HYDROXY METHACRYLATE COATING

Technical Field

The present invention relates to the application of a coating of a poly-hydroxymethacrylate derivative to improve the biocompatibility of metal stents intended for implantation or insertion. More specifically, the present invention relates to the coating of metallic stents with effective amounts of a coating of a poly-hydroxymethacrylate derivative which will drastically increase the thromboresistance of the stent, as well as prevent any significant deposit of protein, or the occurrence of mineral encrustation, and thereby achieve inhibition of restenosis.

Background Art

Advances in medical and surgical technology involving the introduction of implantation of foreign materials, such as stents, catheters, prostheses, etc. into body-tissue make the search for the development of materials that exhibit a long-term biocompatibility more pressing than ever before. A wide range of materials and polymers have been tested and used in medical device applications. These include polyethylene, polypropylene, polyvinylchloride, polyesters, polystyrene, polyurethane, silicone, polysulphone, polyamide, polytetrafluoroethylene, cellulose and its derivatives. Although they have excellent mechanical and physical properties, they were originally developed for the use in industrial manufacturing and not specifically for the biomedical field.

Foremost among the difficulties that need to be addressed within a medical or surgical context are the problems concerning the development of thromboresistant materials and coatings that will resist protein deposits and adverse vessel-wall reactions. Indeed, it is by now well-documented that adverse reactions between foreign or prosthetic surface and blood components, e.g. platelet-activation and thrombogenesis, constitute the single most important factor limiting the use of certain biomaterials. To prevent uncontrolled hemostasis, patients need to be

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treated prophylactically with anti-coagulants, such as heparin or warfarin. In a considerable fraction of these cases, depending on the site of deployment of the implant, the patient needs to continue this medication indefinitely, necessitating a strictly controlled regime of drug-taking which effectively balances the patient on a narrow operational strip flanked by the dual dangers of uncontrolled bleeding on the one hand and the development of an embolism on the other, both obviously equally disastrous outcomes. Even if this treatment can be discontinued after a limited period of time, it complicates the procedure and significantly increases the patient's risk of post-operative bleeding and infection.

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As a matter of fact, some biomedical applications are totally precluded by the thrombogenic potential of stents and/or synthetic polymers. An example of this is the small diameter vascular graft for use in coronary artery bypass. At present, all synthetic materials fail in this application and a patient requiring coronary bypass must first undergo a procedure to remove the saphenous vein from the leg. This vein is subsequently used to carry out the bypass itself. A biocompatible material would have an enormous benefit in this application.

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With regard to the problem of protein deposition, this manifests itself whenever biological fluids come into contact with synthetic surfaces such as glass, steel or polymers. These deposits have an important impact on the course of subsequent events occurring at the surface such as platelet adhesion-activation for blood containing devices, or mineral encrustation on urological stents. The risk of thrombus formation is, in the case of some devices, also accompanied by the additional risk of infection as a result of the adhesion and proliferation of bacteria at the surface of a biomaterial.

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Numerous experiments have been conducted aiming at improving the biocompatibility of stents and surgical implant-devices. Based on the experimental data, one of the most recent suggestions is to use an amphiphilic polyurethane coating on stents (see e.g., De Scheerder et al.: Biocompatibility of biodegradable and non-biodegradable polymer coated stents in porcine peripheral arteries. *Cardiovasc. Intervent. Radiol.* 18:4, Jul-Aug. 1995, pp.227-32).

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Another approach is based on a discovery made by Chapman in the late 1970's [See e.g., Chapman, D., et al.: Biomembranes as models for polymer surfaces. *Biomaterials*. Vol. 7, July 1986, pp. 121-5, 126-31 and 252-8; Durrani, AA, Hayward, JA and Chapman, D : Biomembranes as models for polymer surfaces II; The syntheses of reactive species for covalent coupling of phosphorylcholine to polymer surfaces. *Biomaterials*, 7:2, 1986 Mar, pp. 121-5; Hall, B., et al.: Biomembranes as models for polymer surfaces. *Biomaterials*. Vol. 10, May 1989, p.219-224; and Hayward, JA, et al.: Biomembranes as models for polymer surfaces IV; ESCA analyses of a phosphorylcholine surface covalently bound to hydroxylated substrates. *Biomaterial*, 7:4, 1986 Jul. pp. 252-8], who observed that intact biological membranes are highly successful in preventing inappropriate blood clotting reactions. He went on to show that the phosphorylcholine head group is essential in imparting biocompatibility to the phospholipids in the cell-membrane. Some of the most promising and successful attempts of designing biocompatible coatings to date, try to harness these properties: by covalently binding a phosphorylcholine-group to a metal or polymer they attempt to mimic the external surface of biomembranes.

Disclosure of the Invention

The present invention is based on a different approach. Instead of coating the stent with polyurethane or any of the other polymers cited above, according to the present invention, a coating of a poly-hydroxy methacrylate derivative is applied to a metallic stent which results in a highly biocompatible and thromboresistant coating for said stents.

More particularly, according to the present invention there is now provided a hemo-compatible, restenosis-inhibiting metallic stent, comprising a coating of a poly-hydroxy methacrylate derivative.

The term poly-hydroxy methacrylate derivative, as used herein, is intended to include hydroxy, alkoxy, and dihydroxy, i.e. glycol derivatives.

More specifically, the present invention provides a hemo-compatible, restenosis-inhibiting metallic stent, comprising a coating of a poly-hydroxy methacrylate derivative selected from the group consisting of poly-hydroxyethylmethacrylate (HEMA), poly (hydroxyethoxyethyl methacrylate) (PHEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly (methoxyethyl methacrylate) (PHEMA), poly (methoxyethoxyethyl methacrylate) (PHEMA), poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), poly (ethylene glycol dimethacrylate) (PEGDMA), and mixtures thereof.

In another aspect of the present invention there is now provided a process for producing hemo-compatible, restenosis inhibiting metallic stents including the steps of:

(a) coating a metallic stent with a liquid which contains a hydroxymethacrylate derivative selected from the group consisting of 2-hydroxyethyl-methacrylate; hydroxyethoxyethyl methacrylate, hydroxydiethoxyethyl methacrylate, methoxyethyl methacrylate, methoxyethoxyethyl methacrylate, methoxydiethoxyethyl methacrylate, ethylene glycol dimethacrylate and mixtures thereof;

(b) polymerization of said 2-hydroxy-methacrylate derivative into a polyhydroxymethacrylate derivative selected from the group consisting of poly-hydroxyethylmethacrylate (HEMA), poly (hydroxyethoxyethyl methacrylate) (PHEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly (methoxyethyl methacrylate) (PHEMA), poly (methoxyethoxyethyl methacrylate) (PHEMA), poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), poly (ethylene glycol dimethacrylate) (PEGDMA), and mixtures thereof;

(c) cleaning the stent after polymerization to extract any remaining residues; and

(d) drying the same.

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The present invention also provides a process for producing hemo-compatible bioactive restenosis inhibiting metallic stents, comprising the steps of:

- a) coating a metallic stent with a liquid which contains poly-hydroxyethylmethacrylate in liquid form;
- b) cleaning the stent to extract any remaining residues; and
- c) drying the same.

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Summary of the invention

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Unlike the approach pioneered by Chapman (Ibid), the present invention does not aim at mimicking the cell-membrane directly. Rather, the aimed-for biocompatibility is achieved by applying a coating of a poly-hydroxymethacrylate to the metallic surface of a stent. Current uses of 2-hydroxyethyl-methacrylate (hereinafter referred to as HEMA) or its polymer (hereinafter referred to as PHEMA) include adhesives, artificial nails, lacquers, cosmetic compositions, UV-inks and soft lens applications. Surfaces of plastic devices are modified with PHEMA. Furthermore, it is also used as an anti-adhesive to prevent cell attachment in cell cultures, and as an inducer of trabecular bone in dental implants. As such, its non-toxicity and usefulness in medical and biological applications is well-documented.

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According to the present invention poly-HEMA is used as a biocompatogenic coating for metal stents. This PHEMA coating renders the stents biocompatible by covering the metallic surface with a uniformly distributed layer of strongly polar and hence hydrophilic groups. As stated hereinbefore, in addition to PHEMA, there are other acrylic-type polymers which are poly-hydroxymethacrylate derivatives and which are similar in general structure to PHEMA:

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Among these derivatives are poly (hydroxyethoxyethyl methacrylate) (PHEEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly (methoxyethyl methacrylate) (PMEMA), poly (methoxyethoxyethyl methacrylate) (PMEEMA), poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), and poly

(ethylene glycol dimethacrylate) (PEGDMA). The use of all these polymers and combinations thereof as coating on metallic stents is part of the present invention, although the invention will now be more specifically described with reference to the preferred PHEMA coating, it being understood that the description with regard to PHEMA is also applicable to said other polymeric coatings.

In a first preferred embodiment of the present invention the polymerization of the HEMA takes place directly on the metallic surface of the stent.

In a second preferred embodiment of the present invention the HEMA is polymerized partly before it comes to the surface of the stent.

In U.S. Patent 5,679,400 there is described a method for providing a therapeutic substance into a body lumen which involves providing a stent and applying to the stent a solution which includes a solvent, a polymer dissolved in the solvent and a therapeutic substance dispersed in the solvent. The polymers described in said patent include bioabsorbable polymers such as poly(lactic acid), poly(lactide-co-glycolide) and poly(hydroxybutyrate-co-valerate) and biostable polymers such as polyurethanes, silicones, polyesters, vinyl homopolymers and copolymers, acrylate homopolymers and copolymers, polyethers and cellulose, however said patent does not teach or suggest the specific use of a coating of a polyhydroxymethacrylate derivative to a stent in the substantial absence of a therapeutic component in order to provide restenosis-inhibiting properties to said stent and the only acrylate polymer mentioned in said patent is an ethylene-methyl methacrylate copolymer, listed as one among tens of other named polymers.

Several explanations may be offered for the biocompatogenic nature of PHEMA. One possibility is that the strongly hydrophilic nature of the outside layer of PHEMA attracts a dense water-coat, thus preventing blood-corpuscles to come into direct contact with the stent, an event that normally triggers the thrombogenic reaction (see, e.g., Binderman, I., et al., Grafts of HTR Polymer versus Kiel Bone in Experimental Long Bone Defects in Rats, ASTM, PA 19103).

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Alternatively, it may be the case that polar PHEMA coating attracts the polar moiety on circulating phospholipids which then precipitate under the form of a lipid bilayer. In this instance, biocompatibility would again be a consequence of mimicking the thromboresistance of cell-membranes. If this latter hypothesis turns out to be correct, it underscores the possibility of self-assembly and hence self-repair of the very factor that induces biocompatibility. This is an extremely desirable property for a stent, especially in locations where there are considerable shear forces due to strong blood-circulation, such as heart and main arteries. In addition, PHEMA coated stents prevent adverse cell reaction of the injured site, cell growth, and restenosis.

Whatever the explanation, it has now been found that coating of the metallic surface of stents with PHEMA results in the creation of a stable and highly biocompatible coating which makes the stent thromboresistant and prevents the deposition of protein and adverse vessel-wall reactions, thus vastly increasing their value in surgical procedures.

Thus, the present invention enables the prevention or minimization of restenosis that is evident in some cases with the introduction of metallic stents, by providing hemo-compatible bioactive restenosis-inhibiting metallic stents.

2-Hydroxyethyl methacrylate (HEMA) can be polymerized into poly-HEMA (PHEMA), which is a polymer exhibiting a strongly polar character. PHEMA shows minimal bacterial or cell binding but excellent cell biocompatibility, no protein deposition and no blood clotting. This means that blood plaques which might trigger the development of a potentially fatal thrombus will not be formed. As there is little or no bacterial adhesion, the risk of infections is minimized. PHEMA is a coating which can be used on metal based stents, and which makes these stents biocompatible. The stents can be made of stainless steel, Ti-based alloys, shape memory alloys or any other metal, eventually in combination with synthetic or biological materials. The stents are coated with the hydrophilic HEMA-monomer, which is then polymerized by using dielectric heating, UV light, electron-beam

radiation, gamma-radiation, ozone initiation, X-rays, lasers, visible light, thermal cure or any other means. Thus, said polymerization can be initiated by at least one of photopolymerization, ionic-polymerization, and chemical-polymerization.

After the polymerization procedure, the stent is placed in hot or boiling liquid, e.g. water to remove the remaining monomers. Such stents find applications in e.g. vascular, endo-esophageal and urological stents, as well as for coronary artery bypass surgery or the repair of aneurysms, etc.

In general, the procedure for preparing coated stents according to the present invention is as follows:

A stock solution is prepared by dissolving the 2-hydroxyethyl methacrylate (HEMA), formula $C_6H_{10}O_3$, CAS Number 868-77-9, in ethanol. Other possible solvents are dimethyl sulfoxide (DMSO), propanol, glycerol, ethylene glycol, cyclohexanol, toluene and dimethyl formamide (DMF). It is preferable to use the HEMA in an as pure as possible form, typically better than 98.4%. Typical solutions are made by dissolving 120 mg HEMA in 1 ml 95% ethanol. The dissolving process is helped by shaking the solution and a storage at e.g. 37°C for 12 hrs. A separation of undissolved material can be reached by centrifuging at e.g. 2500 rpm for 30 min. Further dilution with ethanol can be used to produce coatings of various thickness. Polymerization is lightly inhibited by trace amounts of an inhibitor such as the methyl ether of hydroquinone (MEHQ). MEHQ should be present in a concentration within the range of 150 to 300 ppm, preferably 200 ppm. The HEMA can be modified by the addition of a cross linking agent such as triethyleneglycol dimethacrylate, which comprises between about 0.1 and 6% of the HEMA, preferably 5%. Alternatively, tetraethyleneglycol dimethacrylate, diethyleneglycol dimethacrylate and monoethyleneglycol dimethacrylate can be used. A combination of these diesters can also be used.

After wetting the stents with the described solution, they can be air dried in a e.g. sterile environment (sterile lamina flow hood), or when inhibitors are applied, the polymerization can take place by means of a dielectric furnace, UV light or

controlled temperature chamber. The heating provides sufficient free radical activity to overcome the effect of the inhibitor, resulting in polymerization of the coating. The heating step is, e.g. about 1.5 minutes in duration in a dielectric furnace when the upper electrode is positioned about 5 mm above the stent. In order to remove any remaining HEMA monomer and/or traces of the inhibitor after the polymerization step, the stent is boiled in water for about 2 to 3 minutes after cooling down. This procedure will leach out any remaining HEMA monomer and/or inhibitor. After boiling, the stents can be dried at a slightly higher temperature. 2-hydroxyethyl methacrylate can be applied directly to the stent or with the help of a primer such as silanes.

In order to further improve the biocompatibility, the surface modification by selective alkaline hydrolysis was studied. It was found that the thickness of the modified layer can be influenced by the reaction temperature, NaOH concentrations and reaction time.

Using at least 30% NaOH, short reaction times and temperatures of at least 90° C, coatings with carboxylic groups in the surface layer were prepared. This method can be used for obtaining hydrophilic medical coatings with further improved properties and further increased biocompatibility.

The scope of the invention includes the coating with a poly-hydroxymethacrylate derivative of all metallic surfaces of stents of all types, as well for only metallic stents and for the coating of stents formed from the combination of metal with synthetic or biologic tissues.

Description of Preferred Embodiments

While the invention will now be described in connection with certain preferred embodiments in the following examples so that aspects thereof may be more fully understood and appreciated, it is not intended to limit the invention to these particular embodiments. On the contrary, it is intended to cover all alternatives, modifications and equivalents as may be included within the scope of the invention as defined by the appended claims. Thus, the following examples which include preferred embodiments will serve to illustrate the practice of this invention, it being understood that the

particulars shown are by way of example and for purposes of illustrative discussion of preferred embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood description of formulation procedures as well as of the principles and conceptual aspects of the invention.

Example 1

1. A stock solution is prepared by dissolving 120 mg 2-hydroxyethyl methacrylate (HEMA), formula $C_6H_{10}O_3$, CAS Number 868-77-9, in 1 ml 95% ethanol. It is preferable to use the HEMA in an as pure as possible form, typically better than 98.4%.
2. The dissolving process is helped by shaking the solution for 1 hr. and storing at 37 °C for 12 hr.
3. A separation of undissolved material is then reached by centrifuging at 2,500 rpm for 30 min.
4. Polymerization is lightly inhibited by utilizing trace amounts of an inhibitor (2 drops) and the methylether of hydroquinone (MEHQ) is utilized for this purpose.
5. The Palmaz-Schatz stent and a Wiktor stent were used in this particular example. Other stents have been used in other tests.
6. The stents were thoroughly cleaned using laboratory detergents, and washed in warm water.
7. The stents were left to air dry in a sterile environment (sterile lamina flow hood).
8. The stents were then wetted with the solution by dipping them in the solution to the point where their entire surface was submerged in the liquid.
9. Using a specially designed lever, the stents were lifted out of the solution at a rate of 1 mm/sec. This facilitated the uniformity of the coat.
10. The stents were left to air dry in a sterile environment (sterile lamina flow hood).
11. Steps 8-10 were repeated 4 times in order to get the appropriate coating thickness.

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12. The stents were moved to a UV light chamber and radiated for an additional 10 min. The stents were then placed in the chamber in a way that all sides of the stent were no more than 3 cm away from each lamp.

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13. In order to remove any remaining HEMA monomer and/or traces of the inhibitor after the polymerization step, the stent was boiled in water for about 2 to 3 minutes after cooling down.

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14. After boiling, the stents were dried at a slightly higher temperature.

15. The stents were then placed on an angioplasty balloon and were inflated to 85% of their range.

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16. The stents were weighed and examined under a scanning microscope to determine the uniformity of the coat and its attachment to the stent surface.

17. The stents' surface appeared to be completely covered and to a sufficient level of uniformity. Coating adhesion remained intact even under severe stress.

Example 2

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1. A stock solution was prepared by dissolving 120 mg poly-hydroxyethyl methacrylate (PHEMA) IN 1 ML 95% ethanol. It is preferable to use the PHEMA in an as pure as possible form, typically better than 98.4%.

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2. The dissolving process was helped by heating the solution to 75 °C and shaking the solution for 1 hr.

3. A separation of undissolved material was reached by centrifuging at 3.g. 2500 rpm for 30 min.

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4. The Palmaz-Schatz stent and a Wiktor stent were used in this particular example. Other stents have been used in other tests.

5. The stents were thoroughly cleaned using laboratory detergents and washed in warm water.

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6. The stents were left to air dry in a sterile environment (sterile lamina flow hood).

7. The stents were then wetted with the solution by dipping them in the solution to the point where their entire surface was submerged in the liquid.

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8. Using a specially designed lever, the stents were lifted out of the solution at a rate of 1 mm/sec. This facilitated the uniformity of the coat.

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9. The stents were left to air dry in a sterile environment (sterile lamina flow hood) for 15 min.

10. Steps 7-9 were repeated 4 times in order to obtain the appropriate coating thickness.

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11. The stent was boiled in water for about 2 to 3 minutes.

12. After boiling, the stents were then air-dried at a slightly higher temperature.

13. The stents were then placed on an angioplasty balloon and were inflated to 85% of their range.

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14. The stents were weighed and examined under a scanning microscope to determine the uniformity of the coat and its attachment to the stent surface.

15. The stents' surface appeared to be completely covered and to a sufficient level of uniformity. Coating adhesion remained intact even under severe stress.

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It will be evident to those skilled in the art that the invention is not limited to the details of the foregoing illustrative examples and that the present invention may be embodied in other specific forms without departing from the essential attributes thereof, and it is therefore desired that the present embodiments and examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

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Claims

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WHAT IS CLAIMED IS:

1. A hemo-compatible, restenosis-inhibiting metallic stent, comprising a coating of a poly-hydroxy methacrylate derivative.
2. A hemo-compatible, restenosis-inhibiting metallic stent according to claim 1, comprising a coating of a poly-hydroxy methacrylate derivative selected from the group consisting of poly-hydroxyethylmethacrylate (PHEMA), poly (hydroxyethoxyethyl methacrylate) (PHEEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly (methoxyethyl methacrylate) (PMEMA), poly (methoxyethoxyethyl methacrylate) (PMEEMA), poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), poly (ethylene glycol dimethacrylate) (PEGDMA), and mixtures thereof.
3. A process for producing hemo-compatible, restenosis inhibiting metallic stents comprising the steps of:
 - (a) coating a metallic stent with a liquid which contains a hydroxymethacrylate derivative selected from the group consisting of 2-hydroxyethyl-methacrylate; hydroxyethoxyethyl methacrylate, hydroxydiethoxyethyl methacrylate, methoxyethyl methacrylate, methoxyethoxyethyl methacrylate, methoxydiethoxyethyl methacrylate, ethylene glycol dimethacrylate and mixtures thereof;
 - (b) polymerization of said 2-hydroxy-methacrylate derivative into a polyhydroxymethacrylate derivative selected from the group consisting of poly-hydroxyethylmethacrylate (PHEMA), poly (hydroxyethoxyethyl methacrylate) (PHEEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly (methoxyethyl methacrylate) (PMEMA), poly (methoxyethoxyethyl methacrylate) (PMEEMA), poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), poly (ethylene glycol dimethacrylate) (PEGDMA), and mixtures thereof; and
 - (c) cleaning the stent after polymerization to extract any remaining residues.
4. The process of claim 3 wherein the stent is cleaned in warm water.

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5. The process of claim 3 comprising the additional step of adding a cross linking agent.

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6. The process of claim 5, wherein said cross linking agent is present in an amount of about 0.1% to 6% weight relative to the weight of the 2-hydroxyethyl-methacrylate monomer.

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7. The process of claim 3 wherein the stent is first treated with a primer.

8. The process of claim 3 wherein the stent is made from a metal in combination with a polymer.

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9. The process of claim 3 wherein the stent is made from stainless steel.

10. The process of claim 3 wherein the stent is made from a Ti-based alloy.

11. The process of claim 3 wherein the stent is made from a shape memory alloy.

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12. The process of claim 3 wherein the polymerization is carried out at atmospheric pressure.

13. The process of claim 3 wherein the polymerization is carried out by dielectric heating.

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14. The process of claim 3 wherein the polymerization is carried out by induction heating.

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15. The process of claim 3 wherein the polymerization is initiated by at least one of photopolymerization, ionic-polymerization, and chemical-polymerization.

16. The process of claim 3 wherein the polymerization is carried out at elevated pressures.

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17. The process of claim 3 wherein the polymerization is carried out at temperatures in the range of 150°C to 230°C.

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18. The process of claim 5, wherein said cross linking agent is methacrylic diester of ethyleneglycol.

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19. The process of claim 18, wherein said methacrylic diester of ethyleneglycol is selected from the group consisting of:

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- (a) tetraethyleneglycol dimethacrylate,
- (b) triethyleneglycol dimethacrylate,
- (c) diethyleneglycol dimethacrylate,
- (d) monoethyleneglycol dimethacrylate, and
- (e) mixtures thereof.

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20. The process of claim 3, wherein said poly-hydroxyethylmethacrylate comprises a copolymer of monomeric 2-hydroxyethyl-methacrylate.

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21. The process of claim 20, wherein said coating contains a cross linking agent.

22. The process of claim 3 wherein NaOH is added before said polymerization step.

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23. The process of claim 22, wherein said at least 30% NaOH is used.

24. The process of claim 22, wherein said polymerization is effected at a temperature of at least 90°C.

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25. The process of claim 3, comprising diluting said poly-hydroxyethylmethacrylate containing liquid in order to obtain different coating thicknesses.

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26. A process for producing hemo-compatible bioactive restenosis inhibiting metallic stents, comprising the steps of:

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- a) coating a metallic stent with a liquid which contains poly-hydroxyethylmethacrylate in liquid form;
- b) cleaning the stent to extract any remaining toxic residues; and
- c) drying the same.

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/IL 99/00376

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L31/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 2 226 129 A (HUELS CHEMISCHE WERKE AG) 3 July 1998 (1998-07-03) page 15, line 19 -page 16, line 14 page 20, line 23 -page 21, line 3	1-12, 15, 20, 21, 26
X	WO 96 25897 A (MENLO CARE INC) 29 August 1996 (1996-08-29) claims 1, 4, 6, 14	1-12, 15, 20, 21, 26
A	EP 0 574 880 A (UNITED STATES SURGICAL CORP) 22 December 1993 (1993-12-22) page 4, line 46 - line 55 example 4	1-3, 5, 6, 15, 18-21, 26

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"Z" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/IL 99/00376

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: A61L 31/08, A61F 2/06, A61K 51/12, A61L 31/16, A61L 31/18	A1	(11) International Publication Number: WO 00/12147 (43) International Publication Date: 09 March 2000 (09.03.2000)
(21) International Application Number: PCT/US99/19697 (22) International Filing Date: 31 August 1999 (31.08.1999) (30) Priority Data: 09/145,707 02 September 1998 (02.09.1998) US (60) Parent Application or Grant SCIMED LIFE SYSTEMS, INC. [/]; (). YANG, Dachuan [/]; (). WANG, Lixiao [/]; (). ANDERSON, William, E., II; ().	Published	
(54) Title: DRUG DELIVERY DEVICE FOR STENT (54) Titre: SYSTEME D'ADMINISTRATION DE MEDICAMENTS POUR STENT (57) Abstract <p>A device adapted for mounting on a stent, the device comprising a sheath being made of polymeric material that includes drugs such as pharmaceutical agent(s) or radioactive agent(s) for delivery to an implant site. The sheath includes a main body of a generally tubular shape, and may include mounting means for attaching same to the stent. The device may have a slit therein, and may comprise a helical coil, a cylinder or any other suitable shape or design which fits a particular stent. The sheath may include a coating or coatings thereon containing drugs, surgical adhesives or a combination thereof.</p> (57) Abrégé <p>L'invention concerne un dispositif conçu pour être monté sur un stent. Ce dispositif comprend une gaine en matériau polymère contenant des médicaments, par exemple un ou plusieurs agent(s) pharmaceutiques, devant être administrés sur le site d'implantation. Cette gaine comprend un élément principal de forme sensiblement tubulaire et peut comprendre des moyens de fixation permettant de la fixer sur le stent. Le dispositif peut comprendre une fente ainsi qu'un enroulement hélicoïdal, un cylindre ou toute autre forme ou structure adaptée à un stent particulier. La gaine peut en outre comprendre une ou plusieurs couches de revêtement contenant des médicaments, des adhésifs chirurgicaux ou une combinaison des deux.</p>		

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